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(56) References cited:
EP-A- 0 309 297 **US-A- 4 803 261**

- **J.E. RIVIER et al. (eds.), "PEPTIDES", Proceedings of the 11th American Peptide Symposium, 09-14 July 1989, La Jolla, CA (US); 1990, ESCOM, Leiden (NL)**
- **JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 263, no. 11, 15 April 1988; COY et al., pp. 5056-5060**
- **PROCEEDINGS OF THE NATL. ACADEMY OF SCIENCES USA, vol. 82, November 1985, Washington, DC (US); ZACHARY et al., pp. 7616-7620**

EP 0 489 089 B1

Description

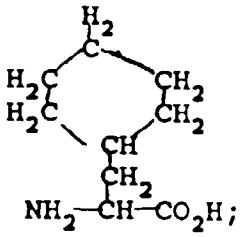
This invention relates to peptides useful, e.g., for treatment of benign or malignant proliferation of tissue, for gastrointestinal disorders, and for diabetes, or pharmaceutically acceptable salts thereof.

The amphibian peptide bombesin, pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2 (Anastasi et al., Experientia 27:166-167 (1971)), is closely related to the mammalian gastrin-releasing peptides (GRP), e.g., the porcine GRP, H_2N-Ala-Pro-Val-Ser-Val-Gly-Gly-Gly-Thr-Val-Leu-Ala-Lys-Met-Tyr-Pro-Arg-Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met-(NH_2) (McDonald et al., Biochem. Biophys. Res. Commun. 90:227-233 (1979)) and human GRP, H_2N-Val-Pro-Leu-Pro-Ala-Gly-Gly-Gly-Thr-Val-Leu-Thr-Lys-Met-Tyr-Pro-Arg-Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met (NH_2). Bombesin has been found to be a growth factor for a number of human cancer cell lines, including small-cell lung carcinoma (SCLC), and has been detected in human breast and prostate cancer (Haveman et al., eds. Recent Results in Cancer Research - Peptide Hormones in Lung Cancer, Springer-Verlag, New York:1986). A number of these cancers are known to secrete peptide hormones related to GRP or bombesin. Consequently, antagonists to bombesin have been proposed as agents for the treatment of these cancers.

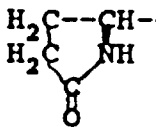
Cuttitta et al. demonstrated that a specific monoclonal antibody to bombesin inhibited in vivo the growth of a human small-cell lung cancer cell line xenografted to nude mice (Cuttitta et al., Cancer Survey 4:707-727 (1985)). In 3T3 murine fibroblasts which are responsive to the mitotic effect of bombesin, Zachary and Rozengurt observed that a substance P antagonist (Spantide) acted as a bombesin antagonist (Zachary et al., Proc. Natl. Acad. Sci. (USA). 82: 7616-7620 (1985)). Heinz-Erian et al. replaced His at position 12 in bombesin with D-Phe and observed bombesin antagonist activity in dispersed acini from guinea pig pancreas (Heinz-Erian et al., Am. J. of Physiol. 252:G439-G442 (1987)). Rivier reported work directed toward restricting the conformational freedom of the bioactive C-terminal decapeptide of bombesin by incorporating intramolecular disulfide bridges; however, Rivier mentioned that, so far, bombesin analogs with this modification fail to exhibit any antagonist activity (Rivier et al., "Competitive Antagonists of Peptide Hormones," in Abstracts of the International Symposium on Bombesin-Like Peptides in Health and Disease, Rome, Italy (October, 1987).

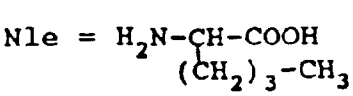
Certain peptide analogues of bombesin and gastrin releasing peptides have, however, been shown to exhibit bombesin antagonist activity, as observed in EP 0 309 297 (The Administrators of the Tulane Educational Fund). Further analogues and their activities are reported in "Peptides - Proceedings of the 11th American Peptide Symposium" July 9-14, 1989, La Jolla, California by Heimbrook et al (p56-59) and Camble et al (p174-176).

Abbreviations (uncommon):

cyclohexyl-Ala =  (cyclohexyl alanine)

identifying group

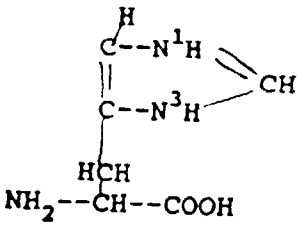
pGlu =  (pyroglutamic acid);

Nle =  (norleucine)

Pal = 3-pyridyl-alanine
β-leu = β - homoleucine
γ-leu = gamma - homoleucine
D-Cpa = D-p-chlorophenylalanine
Met = methionine

HyPro = hydroxyproline
Nal = naphthylalanine
Sar = sarcosine
F_5-Phe = penta-fluoro-Phenylalanine
R = right (D) configuration; S = left (L) configuration; racemate = equal mix of R and S

1-methyl-His; 3-methyl-His = methyl (CH_3) group on nitrogen at positions 1 or 3 of Histidine:

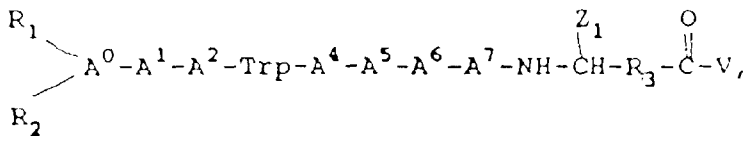


The locations of the modifications that give rise to antagonists are determined by the location of the active site in the naturally occuring peptide. For example, the linear peptides for which introduction of a non-peptide bond between the carboxyl terminal and adjacent amino acid residues, or the replacement of the natural carboxyl terminal and adjacent amino acid residues with a β-, or γ- amino acid residue, or the deletion ("des") of the C-terminal amino acid residue are useful in creating or enhancing antagonist activity are those in which activity is associated with the two C-terminal amino acid residues of the amino acid chain Similarly, where the active site is located in the amino terminal portion of the naturally occuring peptide, the corresponding analogs of the invention will possess modifications in their amino terminal portions.

By non-peptide bond is meant that the carbon atom participating in the bond between two residues is reduced from a carbonyl carbon to a methylene carbon, i.e., CH_2-NH; or, less preferably that CO-NH is replaced with any of CH_2-S, CH_2-O, CH_2-CH_2, CH_2-CO, or CO-CH_2. (A detailed discussion of the chemistry of non-peptide bonds is given in Coy et al. (1988) Tetrahedron 44, 3:835-841, hereby incorporated by reference, Tourwe (1985) Janssen Chim. Acta 3:3-15, 17-18, hereby incorporated by reference, and Spatola (1983) in Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins, (B. Weinstein, ed.) M. Dekker, New York and Basel, pp. 267-357, hereby incorporated by reference.)

One modification of the naturally occurring peptide to create an antagonist is of the amino terminal end of the molecule, such as those described for the amino terminal positions in the generic formula below; for example, the N-terminal amino acid residue, which is A^0 or, if A^0 is deleted, is A^1 or, if A^0 and A^1 are deleted, is A^2 below, may be an aromatic D-isomer, or may be an alkylated amino acid residue. (Where "D" is not designated as the configuration of an amino acid, L is intended; furthermore, where R or S is designated in the generic formulae, the D (R) or L (S) form of an amino acid may occur at any position.

There is provided in accordance with a first aspect of the present invention a compound comprising a peptide having eight or nine amino acid residues, or a pharmaceutically acceptable salt thereof; said peptide being an analog of one of the following naturally occurring peptides terminating at the carboxy-terminus with a Met residue: (a) litorin; (b) the ten amino acid carboxy-terminal region of mammalian gastrin releasing peptide; and (c) the ten amino acid carboxy-terminal region of amphibian bombesin; said peptide being of the formula:



wherein

A^0 = Gly, Nle, α-aminobutyric acid, or the D-isomer of any of Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal, or is deleted;
A^1 = F_5-D-Phe;
A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, β-Nal, His, 1-methyl-His, or 3-methyl-His;
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Iie, Nle, α-aminobutyric acid, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;
A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, p-X-Phe (where X = F, Cl, Br, OH, H or CH_3),

Trp, Thr, or β-Nal;

A^6 = Sar, Gly, Ala, N-methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;

A^7 = 1-methyl-His, 3-methyl-His, or His;

wherein

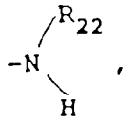
R_3 is CHR_{20}-$(CH_2)_{n1}$ (where R_{20} is either of H or OH; and n1 is either of 1 or 0), or is deleted;

Z_1 is the identifying group of any of the amino acids Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, Gln, p-X-Phe (where X = H, F, Cl, Br, NO_2, OH, or CH_3), F_5-Phe, Trp, Cys, Met, Pro, Hypro, cyclohexyl-Ala, or β-nal;

and V is either OR_4, or

where

R_4 is any of $C_{1\text{-}20}$ alkyl, $C_{3\text{-}20}$ alkenyl, $C_{3\text{-}20}$ alkinyl, phenyl, naphthyl, or $C_{7\text{-}10}$ phenylalkyl, and each R_5, and R_6, independently, is any of H, $C_{1\text{-}12}$ alkyl, $C_{7\text{-}10}$ phenylalkyl, lower acyl, or,



where

R_{22} is any of H, $C_{1\text{-}12}$ alkyl, $C_{7\text{-}10}$ phenylalkyl, or lower acyl; provided that, when one of R_5 or R_6 is $-NHR_{22}$, the other is H;

and further provided that any asymmetric carbon atom can be R, S or a racemic mixture; and further provided that each R_1 and R_2, independently, is H, $C_{1\text{-}12}$ alkyl, $C_{7\text{-}10}$ phenylalkyl, COE_1 (where E_1 is $C_{1\text{-}20}$ alkyl, $C_{3\text{-}20}$ alkenyl, $C_{3\text{-}20}$ alkinyl, phenyl, naphthyl, or $C_{7\text{-}10}$ phenylalkyl) or lower acyl, and R_1 and R_2 are bonded to the N-terminal amino acid of said peptide, and further provided that when one of R_1 or R_2 is COE_1, the other must be H.

in preferred embodiments, the peptide has the formula A^0 = Gly, D-Phe, or is deleted;

A^2 = Leu, Gln, His, 1-methyl-His, or 3-methyl-His;

A^4 = Ala;

A^5 = Val;

A^6 = Sar, Gly, D-Phe, N-methyl-D-Ala, or D-Ala;

A^7 = His;

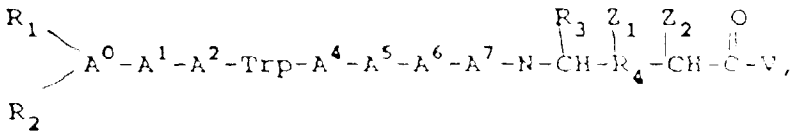
either (1) R_3

is CH_2 or CH_2-CH_2, and Z_1 is the identifying group of Leu or Phe, or (2) R_3 is CHOH-CH_2, and Z_1 is the identifying group of Leu, cyclohexyl-Ala, or Phe and each R_5 and R_6 is H; V is NHR_6, where

R_6 is NH_2; and each R_1 and R_2, independently, is H, lower alkyl, or lower acyl.

Preferably, the peptide is of the formula wherein V is OR_4, and R_4 is any of $C_{1\text{-}20}$ alkyl, $C_{3\text{-}20}$ alkenyl, $C_{3\text{-}20}$ alkinyl, phenyl, naphthyl, or $C_{7\text{-}10}$ phenylalkyl.

The compound in a second and alternative aspect of the invention comprises a peptide having eight or nine amino acid residues, or a pharmaceutically acceptable salt thereof; said peptide being an analog of one of the following naturally occurring peptides terminating at the carboxy-terminus with a Met residue: (a) litorin; (b) the ten amino acid carboxy-terminal region of mammalian gastrin releasing peptide; and (c) the ten amino acid carboxy-terminal region of amphibian bombesin; said peptide being of the formula:



wherein

A^0 = Gly, Nle, α-aminobutyric acid, or the D-isomer of any of Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal, or is deleted;

A^1 = F_5-D-Phe;

A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, β-Nal, His, 1-methyl-His, or 3-methyl-His;

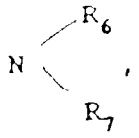
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, α-aminobutyric acid, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;

A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, p-X-Phe (where X = F, Cl, Br, OH, H or CH_3), Trp, Thr, or β-Nal;

A^6 = Sar, Gly, Ala, N-methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;

A^7 = 1-methyl-His, 3-methyl-His, or His;

wherein R_4 is CH_2-NH, CH_2-S, CH_2-O, CO-CH_2, CH_2-CO, or CH_2-CH_2, and each Z_1 and Z_2, independently, can be the identifying group of any one of the amino acids Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, Gln, β-Nal, p-X-Phe (where X = H, F, Cl, Br, NO_2, OH or CH_3), Trp, Cys, Met, Pro, HyPro, or cylcohexyl-Ala; and V is either OR_5 or



where each R_3, R_5, R_6, and R_7, independently, is H, lower alkyl, lower phenylalkyl, or lower naphthylalkyl; provided that any asymmetric carbon atom can be R, S or a racemic mixture; and further provided that each R_1 and R_2, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, COE_1 (where E_1 is C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl), or lower acyl, and R_1 and R_2 are bonded to the N-terminal amino acid of said peptide: and further provided that when one of R_1 or R_2 is COE_1, the other must be H.

In preferred embodiments, the peptide is of the formula

A^0 = Gly, D-Phe, or is deleted;

A^2 = Leu, Gln, His, 1-methyl-His, or 3-methyl-His;

A^4 = Ala;

A^5 = Val;

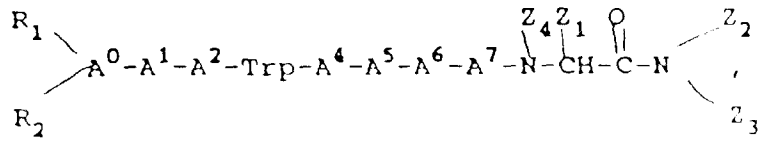
A^6 = Sar, Gly, D-Phe, N-methyl-D-Ala, or D-Ala;

A^7 = His;

R_4 is CH_2-NH or CH_2-O, each Z_1 and Z_2, independently is the identifying group of Leu or Phe; and each R_1 and R_2, independently, is H, lower alkyl, or lower acyl.

Preferably, the analogue is of the formula wherein R_4 is CH_2-NH, and said carbon atom is bonded to Z_2 is of said R configuration.

According to a third alternative aspect of this invention, there is provided a compound comprising a peptide having eight or nine amino acid residues, or a pharmaceutically acceptable salt thereof; said peptide being an analog of one of the following naturally occurring peptides terminating at the carboxy-terminus with a Met residue: (a) litorin; (b) the ten amino acid carboxy-terminal region of mammalian gastrin releasing peptide; and (c) the ten amino acid carboxy-terminal region of amphibian bombesin; said peptide being of the formula:



wherein

A^0 = Gly, Nle, α-aminobutyric acid, or the D-isomer of any of Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal, or is deleted;

A^1 = F_5-D-Phe;

A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, β-Nal, His, 1-methyl-His, or 3-methyl-His;

A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, α-aminobutyric acid, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;

A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, p-X-Phe (where X = F, Cl, Br, OH, H or CH_3), Trp, Thr, or β-Nal;

A^6 = Sar, Gly, Ala, N-methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;

A^7 = 1-methyl-His, 3-methyl-His, or His;

Z_1 is the identifying group of any one of the amino acids Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, β-Nal, Gln, p-X-Phe (where X = H, F, Cl, Br, NO_2, OH or CH_3), F_5-Phe, Trp, Cys, Met, Pro, or HyPro;

and each Z_2, Z_3, and Z_4, independently, is H, lower alkyl, lower phenylalkyl, or lower naphthylalkyl;

further provided that any asymmetric carbon atom can be R, S or a racemic mixture; and further provided that each R_1 and R_2, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl COE_1 (where E_1 is C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl), or lower acyl, and R_1 and R_2 are bonded to the N-terminal amino acid of said peptide; and further provided that when one of R_1 or R_2 is COE_1, the other must be H.

In preferred embodiments, the peptide is of the formula

A^0 = Gly, D-Phe, or is deleted;

A^2 = Leu, Gln, His, 1-methyl-His, or 3-methyl-His;

A^4 = Ala;

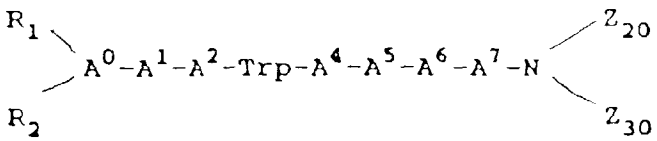
A^5 = Val;

A^6 = Sar, Gly, D-Phe, N-methyl-D-Ala, or D-Ala;

A^7 = His;

where Z_1 is the identifying group of any one of the amino acids Leu, F_5-Phe, or p-X-Phe (where X = H, F, Cl, Br, NO_2, OH or CH_3); and each Z_2, Z_3 and Z_4,
independently, is H, lower alkyl, lower phenylalkyl, or lower naphthylalkyl; and each R_1 and R_2, independently, is H, lower alkyl, or lower acyl.

According to a fourth and yet further alternative aspect of this invention, we provide a compound comprising peptide having between seven and nine amino acid residues, inclusive, or a pharmaceutically acceptable salt thereof, said peptide being an analog of one of the following naturally occurring peptides terminating at the carboxy-terminus with a Met residue: (a) litorin; (b) the ten amino acid carboxy-terminal region of mammalian gastrin releasing peptide; and (c) the ten amino acid carboxy-terminal region of amphibian bombesin; said peptide being of the formula:



wherein

A^0 = Gly, Nle, α-aminobutyric acid, or the D-isomer of any of Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal, or is deleted;

A^1 = F_5-D-Phe;
A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, β-Nal, His, 1-methyl-His, or 3-methyl-His;
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, α-aminobutyric acid, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;
A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, p-X-Phe (where X = F, Cl, Br, OH, H or CH_3), Trp, Thr, or β-Nal;
A^6 = Sar, Gly, Ala, N-methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H, or CH_3), Trp, Cys, or β-Nal;
A^7 = 1-methyl-His, 3-methyl-His, or His;

wherein each Z_{20} and Z_{30}, independently, is H, lower alkyl, lower phenylalkyl, lower naphthylalkyl;
provided that, when either of Z_{20} or Z_{30} is other than H, A^7 is His, A^6 is Gly, A^5 is Val, A^4 is Ala, A^2 is His, and either of R_1 or R_2 is other than H;

further provided that any asymmetric carbon atom can be R, S or a racemic mixture; and further provided that each R_1 and R_2, independently, is H, $C_{1\text{-}12}$ alkyl, $C_{7\text{-}10}$ phenylalkyl, COE_1 (where E_1 is $C_{1\text{-}20}$ alkyl, $C_{3\text{-}20}$ alkenyl, $C_{3\text{-}20}$ alkinyl, phenyl, naphthyl, or $C_{7\text{-}10}$ phenylalkyl), or lower acyl, and R_1 and R_2 are bonded to the N-terminal amino acid of said peptide, and further provided that when one of R_1 or R_2 is COE_1, the other must be H.

In preferred embodiments, the peptide is of the formula

A^0 = Gly, D-Phe, or is deleted;
A^2 = Leu, Gln, His, 1-methyl-His, or 3-methyl-His;
A^4 = Ala;
A^5 = Val;
A^6 = Sar, Gly, D-Phe, N-methyl-D-Ala, or D-Ala;
A^7 = His;

and, where each Z_{20} and Z_{30}, is H; and each R_1 and R_2, independently, is H, lower alkyl, or lower acyl

In other preferred embodiments, the analogue is at least 25% homologous, and preferably at least 50% homologous, with litorin, mammalian gastrin-releasing peptide amphibian bombesin.

Preferred peptides include D-F5-Phe-Gln-Trp-Ala-Val-D-Ala-His-Leu-methylester.

The antagonists described herein are useful for treating diseases involving the malignant or benign proliferation of tissue, such as all forms of cancer where bombesin-related or GRP-related substances act as autocrine or paracrine mitotic factors, e.g., cancers of the gastrointestinal tract, pancreatic cancer, colon cancer, lung cancer, particularly the small cell subtype, prostate or breast cancer; or for treating artherosclerosis, and disorders of gastrointestinal tissues related to gastric and pancreatic secretions and motility; for example, for causing the suppression of amylase secretion, or for appetite control.

In the generic formulae given above, any R or Z group is an aromatic, lipophilic group, the in vivo activity can be long lasting, and delivery of the compounds of the invention to the target tissue can be facilitated.

The identifying group of an α-amino acid is the atom or group of atoms, other than the α-carbonyl carbon atom, the α-amino nitrogen atom, or the H atom, bound to the asymmetric α-carbon atom. To illustrate by examples, the identifying group of alanine is CH_3, the identifying group of valine is $(CH_3)_2CH$, the identifying group of lysine is $H_3N^+(CH_2)_4$ and the identifying group of phenylalanine is $(C_6H_6)CH_2$. The identifying group of a β- or γ-amino acid is the analagous atom or group of atoms bound to respectively, the β- or the γ-carbon atom. Where the identifying group of an amino acid is not specified it may be α, β, or γ.

Other features and advantages will be apparent from the following description of the preferred embodiments thereof.

We first briefly describe the drawing in which the single figure sets out a series of amino acid sequences of naturally occurring peptides of which peptides of the invention are analogues.

Some peptides described herein have a non-peptide bond, namely the carbon atom participating in the bond between two residues is reduced from a carbonyl carbon to a methylene carbon. The peptide bond reduction method which yields this non-peptide bond is described in Coy et al., U.S. patent application, Serial No. 879,348, assigned to the same assignee as the present application, hereby incorporated by reference. Any one of the amino acids in positions 0, and 9 of the litorin antagonists may be deleted from the peptides, and the peptides are still active as antagonists.

Our peptides can be provided in the form of pharmaceutically acceptable salts. Examples of preferred salts are those with therapeutically acceptable organic acids, e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, salicylic, methanesulfonic, toluenesulfonic, or pamoic acid, as well as polymeric acids such as tannic acid or carboxymethyl cellulose, and salts with inorganic acids such as the hydrohalic acids, e.g., hydrochloric acid, sulfuric acid, or

phosphoric acid.

Synthesis of D-F_5- Phe-Gln-Trp-Ala-Val-D-Ala-His(Tos)-Leu-O-Resin is as follows: Alpha-t-butoxycarbonyl(Boc)-Leu-O-Merrifield resin (1.0 g. 0.5 mmole) is placed in the reaction vessel of an Advanced ChemTech ACT 200 automatic peptide synthesizer programmed to perform the following reaction/wash cycle: (a) methylene chloride; (b) 33% trifluoroacetic acid in methylene chloride (2 times for 1 and 25 min. each); (c) propanol; (d) dimethylformamide; (e) 10% triethylamine in dimethylformamide; (f) dimethylformamide.

The neutralized resin is stirred with Boc-N^{im}-tosyl-histidine and diisopropylcarbodiimide (1.5 mmole each) in methylene chloride for 1 h. and the resulting amino acid resin is then cycled through steps (a) to (f) in the above wash program. The Boc group is then removed by TFA treatment. The following amino acids (1.5 mmole) are then coupled successively by the same procedure: Boc-D-Ala, Boc-Val, Boc-Ala, Boc-Trp, Boc-Gln (coupled in the presence of 1 equiv. hydroxybenzotriazole), and Boc-D-F_5-Phe. After the last coupling was complete, the final Boc group was removed by TFA treatment.

Synthesis of D-F_5Phe-Gln-Trp-Ala-Val-D-Ala-His-Leu-methyl ester is as follows.

This peptide is cleaved from the Merrifield resin described above under the same conditions to give 198 mg of the product as a white, fluffy powder; this product is found to be homogeneous by hplc and tlc.

Amino acid analysis of an acid hydrolysate confirms the composition of the octapeptide and fast atom bombardment mass spectrometry gives the expected molecular weight for the peptide. Other bombesin or GRP antagonists can be prepared by making appropriate modifications to the synthetic methods described above.

Other compounds can be prepared as above and tested for effectiveness as agonists or antagonists in the test program described below.

A statine, AHPPA, ACHPA, β-amino acid, or Y-amino acid residue is added in the same way as is a natural α-amino acid residue, by coupling as a Boc derivative.

Phase 1 - 3T3 Peptide Stimulate [^{3}H] Thymidine Uptake Assay

Cell Culture. Stock cultures of Swiss 3T3 cells are grown in Dulbecco's Modified Eagles Medium (DMEM) supplemented with 10% fetal calf serum in humidified atmosphere of 10% CO_2/90% air at 37°C. For experimental use, the cells are seeded into 24-well cluster trays and used four days after the last change of medium. The cells are arrested in the G1/G0 phase of the cell cycle by changing to serum-free DMEM 24 hours prior to the thymidine uptake assay.

Assay of DNA Synthesis. The cells are washed twice with 1ml aliquots of DMEM (-serum) then incubated with DMEM (-serum), 0.5μM [methyl-^{3}H] thymidine (20Ci/mmole, New England Nuclear), bombesin (3nM), and initially four concentrations of the test compounds (1, 10, 100, 1000nM) in a final volume of 1.0 ml. After 28 hours at 37°C, [methyl-^{3}H] thymidine incorporation into acid-insoluble pools is assayed as follows. The cells are washed twice with ice-cold 0.9% NaCl (1ml aliquots), and acid soluble radioactivity is removed by a 30 min. (4°C) incubation with 5% trichloroacetic acid (TCA). The cultures are then washed once (1ml) with 95% ethanol and prepared by homogenization in 50mM TrisHCl containing 0.1% bovine serum albumin and 0.1mg/ml bacitracin followed by two centrifugations (39,000xgx15 min., 4°C) with an intermediate resuspension in fresh buffer. For assay, aliquots (0.8ml) are incubated with 0.5nM [^{125}I]GRP (~2000 Ci/mmol, Amersham Corp.) and various concentrations of the test compounds in a final volume of 0.5ml. After a 30 minute incubation at 4°C, the binding reaction is terminated by rapid filtration through Whatman GF/C filters that have been pre-soaked in 0.3% aqueous polethyleneimine to reduce the level of nonspecific binding. The filters and tubes are washed three times with 4ml aliquots of ice-cold buffer, and the radioactivity trapped on the filters is counted by gamma-spectrometry. Specific binding is defined as the total [^{125}I]GRP bound minus that bound in the presence of 1000nM bombesin or a related peptide.

Phase 5- Inhibition of Gastrin Release

The stomachs of anesthetized rats are perfused with saline collected over 15 minute periods via pyloric cannulation while the test peptide is infused through the femoral vein for periods between 0 and 150 minutes.

Phase 6- In Vivo Antitumor Activity

NCI-H69 small cell lung carcinoma cells were transplanted from in vitro culture by implanting each animal with the equivalent of 5 confluent 75 cm^2 tissue culture flasks in the right flank. In vitro NCI-H69 cells grow as a suspension of cellular aggregates. Therefore, no attempt was made to disaggregate the cell agglomerates by physical or chemical means. Tumor size was calculated as the average of two diameters, i.e., (length and width/2) mm.

Results of Assays of Test Peptides

A number of analogs of bombesin or GRP, each containing a non-peptide bond or a statine, AHPPA, or ACHPA, β-amino acid, or Y-amino acid residue, can be synthesized and tested in one or more of the above-described Phase 1 - 6 assays D-F_5-Phe-Gln-Trp-Ala-Val-D-Ala-His-Leu-methylester was examined for its abilities to displace ^{125}I-labelled bombesin from rat pancreatic acini cells and to inhibit amylase release from these cells produced by bombesin itself. The analogue exhibits potencies in the half-maximal effective dose range of 5-10 nM and is thus a potent bombesin receptor antagonist.

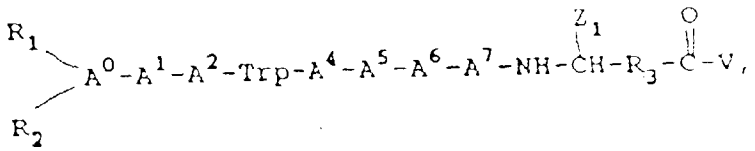
The peptides described herein may be administered to a mammal, particularly a human, in one of the traditional modes (e.g., orally, parenterally, transdermally, or transmucosally), in a sustained release formulation using a biodegradable biocompatible polymer, or by on-site delivery (e.g., in the case of anti-cancer bombesin to the lungs) using micelles, gels and liposomes.

The bombesin antagonists described herein are suitable for the treatment of all forms of cancer where bombesin-related substances act as autocrine or paracrine mitotic agents, particularly small-cell lung carcinoma. The peptides can also be used for the inhibition of gastric acid secretion and motility disorders of the GI tract, the symptomatic relief and/or treatment of exocrine pancreatic adenocarcinoma, and the restoration of appetite to cachexic patients. The peptides can be administered to a human patient in a dosage of 0.5 μg/kg/day to 5 mg/kg/day. For some forms of cancer, e.g., small cell lung carcinoma, the preferred dosage for curative treatment is 250mg/patient/day.

The compound can be administered to a mammal, e.g., a human, in the dosages used for growth hormone releasing factor or, because of their decreased potency, in larger dosages. The compounds can be administred to a mammal, e.g., a human, in a dosage of 0.01 to 1000 mcg/kg/day, preferably 0.1 to 100 mcg/kg/day.

Claims

1. A compound comprising a peptide having eight or nine amino acid residues, or a pharmaceutically acceptable salt thereof; said peptide being an analogue of one of the following naturally occurring peptides terminating at the carboxy-terminus with a Met residue: (a) litorin; (b) the ten amino acid carboxy-terminal region of mammmalian gastrin releasing peptide; and (c) the ten amino acid carboxy-terminal region of amphibian bombesin; said peptide being of the formula:



wherein

A^0 = Gly, Nle, α-aminobutyric acid, or the D-isomer of any of Ala, Val, Gln, Aln, Leu, Ile, Met, p-x-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal, or is deleted;

A^1 = F_5-D-Phe;

A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, β-Nal, His, 1-methyl-His, or 3-methyl-His;

A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, α-aminobutyric acid, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;

A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, p-X-Phe (where X = F, Cl, Br, OH, H or CH_3), Trp, Thr, or β-Nal;

A^6 = Sar, Gly, Ala, N-methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;

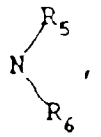
A^7 = 1-methyl-His, 3-methyl-His, or His;

wherein

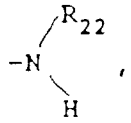
R_3 is CHR_{20}-$(CH_2)_{n1}$ (where R_{20} is either of H or OH; and n1 is either of 1 or 0), or is deleted;

Z_1 is the identifying group of any of the amino acids Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, Gln, p-X-Phe (where X = H, F, Cl, Br, NO_2, OH, or CH_3), F_5-Phe, Trp, Cys, Met, Pro, HyPro, cyclohexyl-Ala, or β-nal;

and V is either OR_4, or



where
R_4 is any of C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl, and each R_5, and R_6, independently, is any of H, C_{1-12} alkyl, C_{7-10} phenylalkyl, lower acyl, or,



where
R_{22} is any of H, C_{1-12} alkyl, C_{7-10} phenylalkyl, or lower acyl; provided that, when one of R_5 or R_6 is $-NHR_{22}$, the other is H;

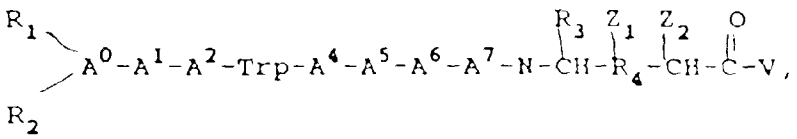
and further provided that any asymmetric carbon atom can be R, S or a racemic mixture; and further provided that each R_1 and R_2, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, COE_1 (where E_1 is C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl), or lower acyl, and R_1 and R_2 are bonded to the N-terminal amino acid of said peptide, and further provided that when one of R_1 or R_2 is COE_1, the other must be H,

2. A compound according to Claim 1, wherein

A^0 = Gly, D-Phe, or is deleted;
A^2 = Leu, Gln, His, 1-methyl-His, or 3-methyl-His;
A^4 = Ala;
A^5 = Val;
A^6 = Sar, Gly, D-Phe, N-methyl-D-Ala, or D-Ala;
A^7 = His;

either (1) R_3 is CH_2 or CH_2-CH_2, and Z_1 is the identifying group of Leu or Phe, or (2) R_3 is CHOH-CH_2, and Z_1 is the identifying group of Leu, cyclohexyl-Ala, or Phe and each R_5 and R_6 is H; V is NHR_6, where R_6 is NH_2; and each R_1 and R_2, independently, is H, lower alkyl, or lower acyl.

3. A compound comprising a peptide having eight or nine amino acid residues, or a pharmaceutically acceptable salt thereof; said peptide being an analog of one of the following naturally occurring peptides terminating at the carboxy-terminus with a Met residue: (a) litorin; (b) the ten amino acid carboxy-terminal region of mammalian gastrin releasing peptide; and (c) the ten amino acid carboxy-terminal region of amphibian bombesin; said peptide being of the formula:



wherein

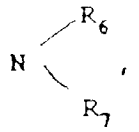
A^0 = Gly, Nle, α-aminobutyric acid, or the D-isomer of any of Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal, or is deleted;
A^1 = F_5-D-Phe;
A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, β-Nal, His, 1-methyl-His, or 3-methyl-His;
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, α-aminobutyric acid, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;
A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, p-X-Phe (where X = F, Cl, Br, OH, H or CH_3),

Trp, Thr, or β-Nal;

A^6 = Sar, Gly, Ala, N-methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;

A^7 = 1-methyl-His, 3-methyl-His, or His;

wherein R_4 is CH_2-NH, CH_2-S, CH_2-O, CO-CH_2, CH_2-CO, or CH_2-CH_2, and each Z_1 and Z_2, independently, can be the identifying group of any one *of* the amino acids Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, Gln, β-Nal, p-X-Phe (where X = H, F, Cl, Br, NO_2, OH or CH_3), Trp, Cys, Met, Pro, HyPro, or cylcohexyl-Ala; and V is either OR_5 or



where each R_3, R_5, R_6, and R_7, independently, is H, lower alkyl, lower phenylalkyl, or lower naphthylalkyl; provided that any asymmetric carbon atom can be R, S or a racemic mixture; and further provided that each R_1 and R_2, independently, is H, $C_{1\text{-}12}$ alkyl, $C_{7\text{-}10}$ phenylalkyl, COE_1 (where E_1 is $C_{1\text{-}20}$ alkyl, $C_{3\text{-}20}$ alkenyl, $C_{3\text{-}20}$ alkinyl, phenyl, naphthyl, or $C_{7\text{-}10}$ phenylalkyl), or lower acyl, and R_1 and R_2 are bonded to the N-terminal amino acid of said peptide; and further provided that when one of R_1 or R_2 is COE_1, the other must be H,

4. A compound according to Claim 3, wherein

A^0 = Gly, D-Phe, or is deleted;

A^2 = Leu, Gln, His, 1-methyl-His, or 3-methyl-His;

A^4 = Ala;

A^5 = Val;

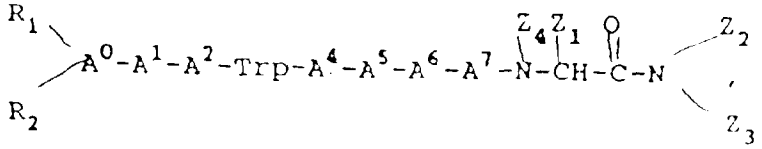
A^6 = Sar, Gly, D-Phe, N-methyl-D-Ala, or D-Ala;

A^7 = His;

where

R_4 is CH_2-NH or CH_2-O, each Z_1 and Z_2, independently is the identifying group of Leu or Phe; and each R_1 and R_2, independently, is H, lower alkyl, or lower acyl.

5. A compound comprising a peptide having eight or nine amino acid residues, or a pharmaceutically acceptable salt thereof; said peptide being an analog of one of the following naturally occurring peptides terminating at the carboxy-terminus with a Met residue: (a) litorin; (b) the ten amino acid carboxy-terminal region of mammalian gastrin releasing peptide; and (c) the ten amino acid carboxy-terminal region of amphibian bombesin; said peptide being of the formula:



wherein

A^0 = Gly, Nle, α-aminobutyric acid, or the D-isomer of any of Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal, or is deleted;

A^1 = F_5-D-Phe;

A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, β-Nal, His, 1-methyl-His, or 3-methyl-His;

A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, α-aminobutyric acid, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;

A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, p-X-Phe (where X = F, Cl, Br, OH, H or CH_3), Trp, Thr, or β-Nal;

A^6 = Sar, Gly, Ala, N-methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;

A^7 = 1-methyl-His, 3-methyl-His, or His;

Z_1 is the identifying group of any one of the amino acids Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, β-Nal, Gln, p-X-Phe (where X = H, F, Cl, Br, NO_2, OH or CH_3), F_5-Phe, Trp, Cys, Met, Pro, or HyPro;
and each Z_2, Z_3, and Z_4, independently, is H, lower alkyl, lower phenylalkyl, or lower naphthylalkyl;

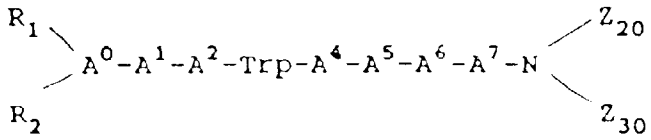
provided that any asymmetric carbon atom can be R, S or a racemic mixture; and further provided that each R_1 and R_2, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl COE_1 (where E_1 is C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl), or lower acyl, and R_1 and R_2 are bonded to the N-terminal amino acid of said peptide and further provided that when one of R_1 or R_2 is COE_1, the other must be H.

6. A compound according to Claim 5, wherein

A^0 = Gly, D-Phe, or is deleted;
A^2 = Leu, Gln, His, 1-methyl-His, or 3-methyl-His;
A^4 = Ala;
A^5 = Val;
A^6 = Sar, Gly, D-Phe, N-methyl-D-Ala, or D-Ala;
A^7 = His;

where Z_1 is the identifying group of any one of the amino acids Leu, F_5-Phe, or p-X-Phe (where X = H, F, Cl, Br, NO_2, OH or CH_3); and each Z_2, Z_3 and Z_4,
independently, is H, lower alkyl, lower phenylalkyl, or lower naphthylalkyl; and each R_1 and R_2, independently, is H, lower alkyl, or lower acyl.

7. A compound comprising a peptide having seven or eight amino acid residues, or a pharmaceutically acceptable salt thereof; said peptide being an analog of one of the following naturally occurring peptides terminating at the carboxy-terminus with a Met residue: (a) litorin; (b) the ten amino acid carboxy-terminal region of mammalian gastrin releasing peptide; and (c) the ten amino acid carboxy-terminal region of amphibian bombesin; said peptide being of the formula:



wherein

A^0 = Gly, Nle, α-aminobutyric acid, or the D-isomer of any of Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal, or is deleted;
A^1 = F_5-D-Phe;
A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, β-Nal, His, 1-methyl-His, or 3-methyl-His;
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, α-aminobutyric acid, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H or CH_3), Trp, Cys, or β-Nal;
A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-aminobutyric acid, Met, Val, p-X-Phe (where X = F, Cl, Br, OH, H or CH_3), Trp, Thr, or β-Nal;
A^6 = Sar, Gly, Ala, N-methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (where X = F, Cl, Br, NO_2, OH, H, or CH_3), Trp, Cys, or β-Nal;
A^7 = 1-methyl-His, 3-methyl-His, or His;

wherein each Z_{20} and Z_{30}, independently, is H, lower alkyl, lower phenylalkyl, lower naphthylalkyl;
provided that, when either of Z_{20} or Z_{30} is other than H, A^7 is His, A^6 is Gly, A^5 is Val, A^4 is Ala, A^2 is His, and either of R_1 or R_2 is other than H;
further provided that any asymmetric carbon atom can be R, S or a racemic mixture; and further provided that each R_1 and R_2, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, COE_1 (where E_1 is C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl), or lower acyl, and R_1 and R_2 are bonded to the N-terminal amino acid of said peptide, and further provided that when one of R_1 or R_2 is COE_1, the other must be H.

8. A compound according to claim 7, wherein

A^0 = Gly, D-Phe, or is deleted;
A^2 = Leu, Gln, His, 1-methyl-His, or 3-methyl-His;
A^4 = Ala;
A^5 = Val;
A^6 = Sar, Gly, D-Phe, N-methyl-D-Ala, or D-Ala;
A^7 = His;

and, where each Z_{20} and Z_{30} is H; and each R_1 and R_2, independently, is H, lower alkyl, or lower acyl.

9. A compound according to any one of Claims 1, 3, 5 and 7, wherein said analogue is at least 25% homologous, and preferably at least 50% homologous with litorin, mammalian gastrin-releasing peptide, or amphibian bombesin.

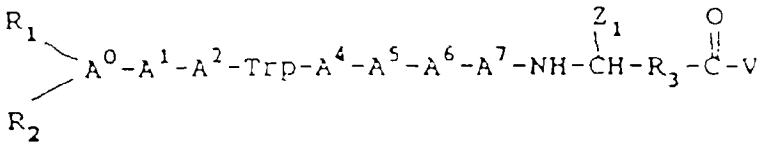
10. A compound according to Claim 3, wherein R_4 is CH_2-NH, and the carbon atom bonded to Z_2 is of R configuration.

11. A compound according to Claim 1, wherein V is OR_4, and R_4 is any of C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl.

12. A compound according to Claim 11, wherein said peptide has the formula D-F_5-Phe-Gln-Trp-Ala-Val-D-Ala-His-Leu-methylester.

Patentansprüche

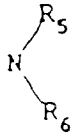
1. Verbindung, die ein Peptid mit acht oder neuen Aminosäureresten oder ein pharmazeutisch nutzbares Salz davon umfaßt, wobei das Peptid ein Analoges eines der folgenden, natürlich vorkommenden Peptide ist, die an ihrer Carboxylterminalposition einen Met-Rest aufweisen: (a) Litorin, (b) der 10-Aminosäure-Carboxylterminalbereich von Säugetiergastrin-Releasing-Peptid und (c) der 10-Aminosäure-Carboxylterminalbereich von Amphibienbombesin; wobei das Peptid die Formel



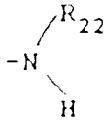
hat, worin

A^0 = Gly, Nle, α-Aminobuttersäure oder das D-Isomer von Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal oder wegfällt;
A^1 = F_5-D-Phe;
A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys, β-Nal, His, 1-Methyl-His oder 3-Methyl-His);
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, α-Aminobuttersäure, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal;
A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-Aminobuttersäure, Met, Val, p-X-Phe (wobei X = F, Cl, Br, OH, H oder CH_3), Trp, Thr oder β-Nal;
A^6 = Sar, Gly, Ala, N-Methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal;
A^7 = 1-Methyl-His, 3-Methyl-His oder His;

worin R_3 für CHR_{20}-$(CH_2)_{n1}$ steht (wobei R_{20} entweder H oder OH bedeutet und n1 entweder 1 oder 0 bedeutet) oder wegfällt;
Z_1 die charakteristische Gruppe einer der Aminosäuren Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, Gln, p-X-Phe (wobei X = H, F, Cl, Br, NO_2, OH oder CH_3), F_5-Phe, Trp, Cys, Met, Pro, HyPro, Cyclohexyl-Ala oder β-Nal ist; und V entweder OR_4 oder



bedeutet, worin R_4 für C_{1-20}Alkyl, C_{3-20}Alkenyl, C_{3-20}Alkinyl, Phenyl, Naphthyl oder C_{7-10}Phenylalkyl steht und R_5 und R_6 jeweils unabhängig voneinander H, C_{1-12}Alkyl, C_{1-12}Phenylalkyl, niederes Acyl oder



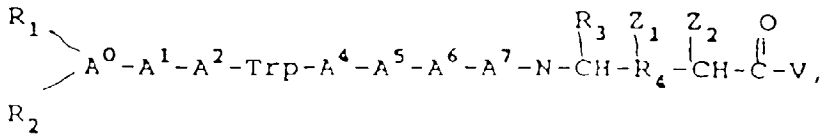
bedeutet, wobei R_{22} für H, C_{1-12}Alkyl, C_{7-10}Phenylalkyl oder niederes Acyl steht; vorausgesetzt, daß, wenn R_5 bzw. R_6 für $-NHR_{22}$ steht, das jeweils andere H ist;
und weiterhin vorausgesetzt, daß es sich bei einem beliebigen asymmetrischen Kohlenstoffatom um R, S oder eine racemische Mischung handeln kann; und darüber hinaus vorausgesetzt, daß R_1 und R_2 jeweils unabhängig voneinander H, C_{1-12}Alkyl, C_{7-10}Phenylalkyl, COE_1 (wobei E_1 = C_{1-20}Alkyl, C_{3-20}Alkenyl, C_{3-20}Alkinyl, Phenyl, Naphthyl oder C_{7-10}Phenylalkyl) oder niederes Acyl bedeuten und R_1 und R_2 an die N-terminale Aminosäure dieses Peptids gebunden sind, und außerdem vorausgesetzt, daß, wenn R_1 bzw. R_2 für COE_1 steht, das jeweils andere H sein muß.

2. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß

A^0 = Gly oder D-Phe oder wegfällt;
A^2 = Leu, Gln, His, 1-Methyl-His oder 3-Methyl-His;
A^4 = Ala;
A^5 = Val;
A^7 = His;

entweder (1) R_3 für CH_2 oder CH_2-CH_2 steht und Z_1 die charakteristische Gruppe von Leu oder Phe bedeutet, oder (2) R_3 für CHOH-CH_2 steht und Z_1 die charakteristische Gruppe von Leu, Cyclohexyl-Ala oder Phe bedeutet und R_5 und R_6 jeweils H bedeuten;
V für NHR_6 steht, wobei R_6 für NH_2 steht und R_1 und R_2 jeweils unabhängig voneinander H, niederes Alkyl oder niederes Acyl bedeuten.

3. Verbindung, die ein Peptid mit acht oder neuen Aminosäureresten oder ein pharmazeutisch nutzbares Salz davon umfaßt, wobei das Peptid ein Analoges eines der folgenden, natürlich vorkommenden Peptide ist, die an ihrer Carboxylterminalposition einen Met-Rest aufweisen: (a) Litorin, (b) der 10-Aminosäure-Carboxylterminalbereich von Säugetiergastrin-Releasing-Peptid; und (c) der 10-Aminosäure-Carboxylterminalbereich von Amphibienbombesin; wobei das Peptid die Formel



hat, worin

A^0 = Gly, Nle, α-Aminobuttersäure oder das D-Isomer von Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal oder wegfällt;
A^1 = F_5-D-Phe;
A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys, β-Nal, His, 1-Methyl-His oder 3-Methyl-His);
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, α-Aminobuttersäure, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal;
A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-Aminobuttersäure, Met, Val, p-X-Phe (wobei X = F, Cl, Br, OH, H oder

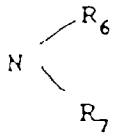
CH_3), Trp, Thr oder β-Nal;

A^6 = Sar, Gly, Ala, N-Methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal;

A^7 = 1-Methyl-His, 3-Methyl-His oder His;

worin R_4 für CH_2-NH, CH_2-S, CH_2-O, CO-CH_2, CH_2-CO oder CH_2-CH_2 steht und Z_1 und Z_2 jeweils unabhängig voneinander die charakteristischen Gruppen einer der Aminosäuren Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, Gln, β-Nal, p-X-Phe (wobei X = H, F, Cl, Br, NO_2, OH oder CH_3), Trp, Cys, Met, Pro, HyPro oder Cyclohexyl-Ala bedeuten;

und V entweder OR_5 oder



bedeutet, wobei R_3, R_5, R_6 und R_7 jeweils unabhängig voneinander niederes Alkyl, niederes Phenylalkyl oder niederes Naphthylalkyl bedeuten;

vorausgesetzt, daß es sich bei einem beliebigen asymmetrischen Kohlenstoffatom um R, S oder eine racemische Mischung handeln kann; und weiterhin vorausgesetzt, daß R_1 und R_2 jeweils unabhängig voneinander H, $C_{1\text{-}12}$Alkyl, $C_{7\text{-}10}$Phenylalkyl, COE_1 (wobei E_1 = $C_{1\text{-}20}$Alkyl, $C_{3\text{-}20}$Alkenyl, $C_{3\text{-}20}$Alkinyl, Phenyl, Naphthyl oder $C_{7\text{-}10}$Phenylalkyl) oder niederes Acyl bedeuten und R_1 und R_2 an die N-terminale Aminosäure dieses Peptids gebunden sind, und außerdem vorausgesetzt, daß, wenn R_1 oder R_2 für COE_1 steht, das jeweils andere H sein muß.

4. Verbindung nach Anspruch 3, dadurch gekennzeichnet, daß

A^0 = Gly oder D-Phe oder wegfällt;

A^2 = Leu, Gln, His, 1-Methyl-His oder 3-Methyl-His;

A^4 = Ala;

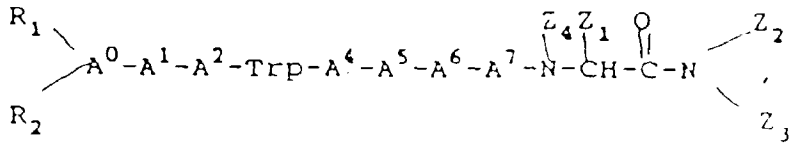
A^5 = Val;

A^6 = Sar, Gly, D-Phe, N-Methyl-D-Ala oder D-Ala;

A^7 = His;

worin R_4 für CH_2-NH oder CH_2-O steht und Z_1 und Z_2 jeweils unabhängig voneinander die charakteristischen Gruppen von Leu oder Phe sind; und R_1 und R_2 jeweils unabhängig voneinander H, niederes Alkyl oder niederes Acyl bedeuten.

5. Verbindung, die ein Peptid mit acht oder neun Aminosäureresten oder ein pharmazeutisch nutzbares Salz davon umfaßt; wobei das Peptid ein Analoges eines der folgenden, natürlich vorkommenden Peptide ist, die an ihrer Carboxylterminalposition einen Met-Rest aufweisen: (a) Litorin, (b) der 10-Aminosäure-Carboxylterminalbereich von Säugetiergastrin-Releasing-Peptid und (c) der 10-Aminosäure-Carboxylterminalbereich von Amphibienbombesin; wobei das Peptid die Formel



hat, worin

A^0 = Gly, Nle, α-Aminobuttersäure oder das D-Isomer von Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal oder wegfällt;

A^1 = F_5-D-Phe;

A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys, β-Nal, His, 1-Methyl-His oder 3-Methyl-His;

A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, α-Aminobuttersäure, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal;

A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-Aminobuttersäure, Met, Val, p-X-Phe (wobei X = F, Cl, Br, OH, H oder CH_3), Trp, Thr oder β-Nal;
A^6 = Sar, Gly, Ala, N-Methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal;
A^7 = 1-Methyl-His, 3-Methyl-His oder His;

Z_1 die charakteristische Gruppe einer der Aminosäuren Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, β-Nal, Gln, p-X-Phe (wobei X = H, F, Cl, Br, NO_2, OH oder CH_3), F_5-Phe, Trp, Cys, Met, Pro oder HyPro ist; und Z_2, Z_3 und Z_4 jeweils unabhängig voneinander H, niederes Alkyl, niederes Phenylalkyl oder niederes Naphthylalkyl bedeuten;

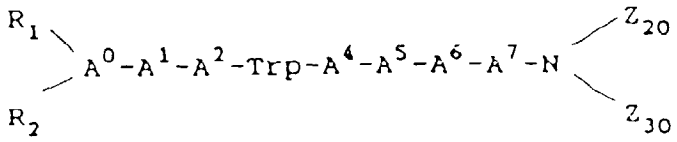
vorausgesetzt, daß es sich bei einem beliebigen asymmetrischen Kohlenstoffatom um R, S oder eine racemische Mischung handeln kann; und weiterhin vorausgesetzt, daß R_1 und R_2 jeweils unabhängig voneinander H, $C_{1\text{-}12}$Alkyl, $C_{7\text{-}10}$Phenylalkyl, COE_1 (wobei E_1 = $C_{1\text{-}20}$Alkyl, $C_{3\text{-}20}$Alkenyl, $C_{3\text{-}20}$Alkinyl, Phenyl, Naphthyl oder $C_{7\text{-}10}$Phenylalkyl) oder niederes Acyl bedeuten und R_1 und R_2 an die N-terminale Aminosäure dieses Peptids gebunden sind, und außerdem vorausgesetzt, daß. wenn R_1 oder R_2 für COE_1 steht. das jeweils andere H sein muß.

6. Verbindung nach Anspruch 5, dadurch gekennzeichnet, daß

A^0 = Gly oder D-Phe oder wegfällt;
A^2 = Leu, Gln, His, 1-Methyl-His oder 3-Methyl-His;
A^4 = Ala;
A^5 = Val;
A^6 = Sar, Gly, D-Phe, N-Methyl-D-Ala oder D-Ala;
A^7 = His;

wobei Z_1 die charakteristische Gruppe einer der Aminosäuren Leu, F_5-Phe oder p-X-Phe (wobei X = H, F, Cl, Br, NO_2, OH oder CH_3) ist und Z_2, Z_3 und Z_4 jeweils unabhängig voneinander H, niederes Alkyl, niederes Phenylalkyl oder niederes Naphthylalkyl bedeuten; und R_1 und R_2 jeweils unabhängig voneinander H, niederes Alkyl oder niederes Acyl bedeuten.

7. Verbindung, die ein Peptid mit sieben oder acht Aminosäureresten oder ein pharmazeutisch nutzbares Salz davon umfaßt, wobei das Peptid ein Analoges eines der folgenden, natürlich vorkommenden Peptide ist, die an ihrer Carboxylterminalposition einen Met-Rest aufweisen: (a) Litorin; (b) der 10-Aminosäure-Carboxylterminalbereich von Säugetiergastrin-Releasing-Peptid und (c) der 10-Aminosäure-Carboxylterminalbereich von Amphibienbombesin; wobei das Peptid die Formel



hat, worin

A^0 = Gly, Nle, α-Aminobuttersäure oder das D-Isomer von Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal oder wegfällt;
A^1 = F_5-D-Phe:
A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys, β-Nal, His, 1-Methyl-His oder 3-Methyl-His);
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, α-Aminobuttersäure, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal;
A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, α-Aminobuttersäure, Met, Val, p-X-Phe (wobei X = F, Cl, Br, OH, H oder CH_3), Trp, Thr oder β-Nal;
A^6 = Sar, Gly, Ala, N-Methyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (wobei X = F, Cl, Br, NO_2, OH, H oder CH_3), Trp, Cys oder β-Nal;
A^7 = 1-Methyl-His, 3-Methyl-His oder His;

worin Z_{20} und Z_{30} jeweils unabhängig voneinander H, niederes Alkyl, niederes Phenylalkyl oder niederes Naphthylalkyl bedeuten;

vorausgesetzt, daß, wenn weder Z_{20} noch Z_{30} für H stehen, bedeutet A^7 = His, A^6 = Gly, A^5 = Val, A^4 = Ala, A^2 = His, und weder R_1 noch R_2 sind H;
und weiterhin vorausgesetzt, daß es sich bei einem beliebigen asymmetrischen Kohlenstoffatom um R, S oder eine racemische Mischung handeln kann; und darüber hinaus vorausgesetzt, daß R_1 und R_2 jeweils unabhängig voneinander H, C_{1-12}Alkyl, C_{7-10}Phenylalkyl, COE_1 (wobei E_1 = C_{1-20}Alkyl, C_{3-20}Alkenyl, C_{3-20}Alkinyl, Phenyl, Naphthyl oder C_{7-10}Phenylalkyl) oder niederes Acyl bedeuten und R_1 und R_2 an die N-terminale Aminosäure dieses Peptids gebunden sind, und außerdem vorausgesetzt, daß, wenn R_1 oder R_2 COE_1 ist, das jeweils andere H sein muß.

8. Verbindung nach Anspruch 7, dadurch gekennzeichnet, daß

A^0 = Gly oder D-Phe oder wegfällt;
A^2 = Leu, Gln, His, 1-Methyl-His oder 3-Methyl-His;
A^4 = Ala;
A^5 = Val;
A^6 = Sar, Gly, D-Phe, N-Methyl-D-Ala oder D-Ala;
A^7 = His;

und wobei Z_{20} und Z_{30} jeweils H bedeuten und R_1 und R_2 jeweils unabhängig voneinander H, niederes Alkyl oder niederes Acyl bedeuten.

9. Verbindung nach einem der Ansprüche 1, 3, 5 und 7, dadurch gekennzeichnet, daß besagtes Analoges zu mindestens 25 % homolog ist und vorzugsweise zu mindestens 50 % homolog mit Litorin, Säugetiergastrin-Releasing-Peptid bzw. Amphibienbombesin ist.

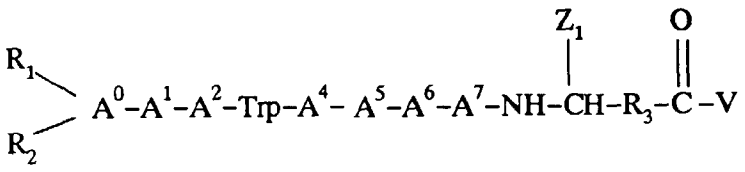
10. Verbindung nach Anspruch 3, dadurch gekennzeichnet, daß R_4 für CH_2-NH steht und das an Z_2 gebundene Kohlenstoffatom eine R-Konfiguration aufweist.

11. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß V für OR_4 steht und R_4 für C_{1-20}Alkyl, C_{3-20}Alkenyl, C_{3-20}Alkinyl, Phenyl, Naphthyl oder C_{7-10}Phenylalkyl steht.

12. Verbindung nach Anspruch 11, dadurch gekennzeichnet, daß das besagte Peptid die Formel
D-F_5-Phe-Gln-Trp-Ala-Val-D-Ala-His-Leu-Methylester hat.

Revendications

1. Composé comprenant un peptide ayant 8 ou 9 résidus d'acides aminés, ou un sel pharmaceutiquement acceptable de celui-ci, ledit peptide étant un analogue de l'un des peptides naturels suivants qui se terminent au niveau de l'extrémité carboxy-terminale par un résidu Met: (a) la litorine, (b) la région carboxy-terminale de 10 acides aminés du peptide libérant la gastrine de mammifère, et (c) la région carboxy-terminale de 10 acides aminés de la bombésine d'amphibien, ledit peptide étant de formule :

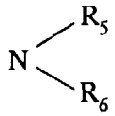


dans laquelle

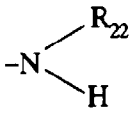
A^0 = Gly, Nle, acide α-aminobutyrique ou l'isomère D de l'un quelconque des acides aminés Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal, ou est délété ;
A^1 = F_5-D-Phe ;
A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys, β-Nal, His, 1-méthyl-His ou 3-méthyl-His;
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, acide α-aminobutyrique, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal ;

A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, acide α-aminobutyrique, Met, Val, p-X-Phe (où X = F, Cl, Br, OH, H ou CH_3), Trp, Thr ou β-Nal ;
A^6 = Sar, Gly, Ala, N-méthyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal ;
A^7 = 1-méthyl-His, 3-méthyl-His ou His ;

où R_3 est CHR_{20}-$(CH_2)_{n1}$ (où R_{20} est H ou OH, et n1 est 1 ou 0), ou est délété ; Z_1 est le groupe identificateur de l'un quelconque des acides aminés Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, Gln, p-X-Phe (où X = H, F, Cl, Br, NO_2, OH ou CH_3), F_5-Phe, Trp, Cys, Met, Pro, HyPro, cyclohexyl-Ala ou β-Nal ;
et V est OR_4 ou



où R_4 est un groupe quelconque parmi alkyle en C_1-C_{20}, alcényle en C_3-C_{20}, alcynyle en C_3-C_{20}, phényle, naphtyle ou phénylalkyle en C_7-C_{10}, et chaque substituant R_5 et R_6, indépendamment, est l'un quelconque des groupes H, alkyle en C_1-C_{12}, phénylalkyle en C_7-C_{10}, acyle inférieur ou



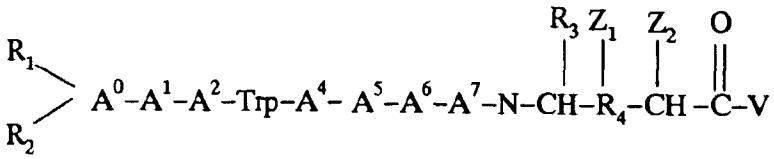
où R_{22} est l'un quelconque des groupes H, alkyle en C_1-C_{12}, phénylalkyle en C_7-C_{10} ou acyle inférieur, à condition que, lorsque l'un des substituants R_5 ou R_6 est -NHR_{22}, l'autre soit H, et à condition également que tout atome de carbone asymétrique puisse être R, S ou un mélange racémique, et à condition encore que chaque substituant R_1 et R_2, indépendamment, soit H, alkyle en C_1-C_{12}, phénylalkyle en C_7-C_{10}, COE_1 (où E_1 est alkyle en C_1-C_{20}, alcényle en C_3-C_{20}, alcynyle en C_3-C_{20}, phényle, naphtyle ou phénylalkyle en C_7-C_{10}), ou acyle inférieur, et que R_1 et R_2 soient liés à l'acide aminé N-terminal dudit peptide, et à condition encore que lorsque l'un des substituants R_1 ou R_2 est COE_1, l'autre doit être H.

2. Composé selon la revendication 1, dans lequel A^0 = Gly, D-Phe ou est délété ;

A^2 = Leu, Gln, His, 1-méthyl-His ou 3-méthyl-His ;
A^4 = Ala ;
A^5 = Val ;
A^6 = Sar, Gly, D-Phe, N-méthyl-D-Ala ou D-Ala ;
A^7 = His ;

(1) R_3 est CH_2 ou CH_2-CH_2 et Z_1 est le groupe identificateur de Leu ou Phe, ou (2) R_3 est CHOH-CH_2 et Z_1 est le groupe identificateur de Leu, cyclohexyl-Ala ou Phe et chaque substituant R_5 et R_6 est H ;
V est NHR_6 où
R_6 est NH_2, et chaque substituant R_1 et R_2, indépendamment, est H, alkyle inférieur ou acyle inférieur.

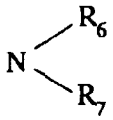
3. Composé comprenant un peptide ayant 8 ou 9 résidus d'acides aminés, ou un sel pharmaceutiquement acceptable de celui-ci, ledit peptide étant un analogue de l'un des peptides naturels suivants qui se terminent au niveau de l'extrémité carboxy-terminale par un résidu Met: (a) la litorine, (b) la région carboxy-terminale de 10 acides aminés du peptide libérant la gastrine de mammifère, et (c) la région carboxy-terminale de 10 acides aminés de la bombésine d'amphibien, ledit peptide étant de formule :



dans laquelle

A^0 = Gly, Nle, acide α-aminobutyrique ou l'isomère D de l'un quelconque des acides aminés Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal, ou est délété ;
A^1 = F_5-D-Phe ;
A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys, β-Nal, His, 1-méthyl-His ou 3-méthyl-His ;
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, acide α-aminobutyrique, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal ;
A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, acide α-aminobutyrique, Met, Val, p-X-Phe (où X = F, Cl, Br, OH, H ou CH_3), Trp, Thr ou β-Nal ;
A^6 = Sar, Gly, Ala, N-méthyl-Ala, Val, Gln, Asn, lieu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal ;
A^7 = 1-méthyl-His, 3-méthyl-His ou His ;

où R_4 est CH_2-NH, CH_2-S, CH_2-O, CO-CH_2, CH_2-CO ou CH_2-CH_2, et chaque substituant Z_1 et Z_2, indépendamment, peut être le groupe identificateur de l'un quelconque des acides aminés Gly, Ala, Val, lieu, Ile, Ser, Asp, Asn, Glu, Gln, β-Nal, p-X-Phe (où X = H, F, Cl, Br, NO_2, OH ou CH_3), Trp, Cys, Met, Pro, HyPro ou cyclohexyl-Ala; et V est OR_5 ou



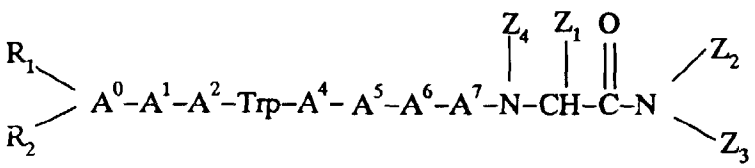
où chaque substituant R_3, R_5, R_6 et R_7, indépendamment, est H, alkyle inférieur, phénylalkyle inférieur ou naphtylalkyle inférieur ;
à condition que tout atome de carbone asymétrique puisse être R, S ou un mélange racémique, et à condition également que chaque substituant R_1 et R_2, indépendamment, soit H, alkyle en C_1-C_{12}, phénylalkyle en C_7-C_{10}, COE_1 (où E_1 est alkyle en C_1-C_{20}, alcényle en C_3-C_{20}, alcynyle en C_3-C_{20}, phényle, naphtyle ou phénylalkyle en C_7-C_{10}), ou acyle inférieur, et que R_1 et R_2 soient liés à l'acide aminé N-terminal dudit peptide, et à condition en outre que lorsque l'un des substituants R_1 ou R_2 est COE_1, l'autre doit être H.

4. Composé selon la revendication 3, dans lequel

A^0 = Gly, D-Phe ou est délété ;
A^2 = Leu, Gln, His, 1-méthyl-His ou 3-méthyl-His ;
A^4 = Ala ;
A^5 = Val ;
A^6 = Sar, Gly, D-Phe, N-méthyl-D-Ala ou D-Ala ;
A^7 = His ;

où
R_4 est CH_2-NH ou CH_2-O, chaque substituant Z_1 et Z_2, indépendamment, est le groupe identificateur de Leu ou Phe, et chaque substituant R_1 et R_2, indépendamment, est H, alkyle inférieur ou acyle inférieur.

5. Composé comprenant un peptide ayant 8 ou 9 résidus d'acides aminés, ou un sel pharmaceutiquement acceptable de celui-ci, ledit peptide étant un analogue de l'un des peptides naturels suivants qui se terminent au niveau de l'extrémité carboxy-terminale par un résidu Met: (a) la litorine, (b) la région carboxy-terminale de 10 acides aminés du peptide libérant la gastrine de mammifère, et (c) la région carboxy-terminale de 10 acides aminés de la bombésine d'amphibien, ledit peptide étant de formule :



dans laquelle

A^0 = Gly, Nle, acide α-aminobutyrique ou l'isomère D de l'un quelconque des acides aminés Ala, Val, Gln,

Asn, Leu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal, ou est délété ;
A^1 = F_5-D-Phe ;
A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys, β-Nal, His, 1-méthyl-His ou 3-méthyl-His ;
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Nle, acide α-aminobutyrique, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal ;
A^5 = Gln, Asn, Gly, Ala, Leu, Ile, Nle, acide α-aminobutyrique, Met, Val, p-X-Phe (où X = F, Cl, Br, OH, H ou CH_3), Trp, Thr ou β-Nal ;
A^6 = Sar, Gly, Ala, N-méthyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal ;
A^7 = 1-méthyl-His, 3-méthyl-His ou His ;

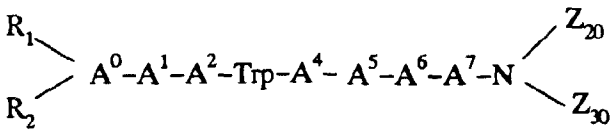
Z_1 est le groupe identificateur de l'un quelconque des acides aminés Gly, Ala, Val, Leu, Ile, Ser, Asp, Asn, Glu, β-Nal, Gln, p-X-Phe (où X = H, F, Cl, Br, NO_2, OH ou CH_3), F_5-Phe, Trp, Cys, Met, Pro ou HyPro ;
et chaque substituant Z_2, Z_3 et Z_4, indépendamment, est H, alkyle inférieur, phénylalkyle inférieur ou naphtylalkyle inférieur;
à condition que tout atome de carbone asymétrique puisse être R, S ou un mélange racémique, et à condition également que chaque substituant R_1 et R_2, indépendamment, soit H, alkyle en C_1-C_{12}, phénylalkyle en C_7-C_{10}, COE_1 (où E_1 est alkyle en C_1-C_{20}, alcényle en C_3-C_{20}, alcynyle en C_3-C_{20}, phényle, naphtyle ou phénylalkyle en C_7-C_{10}), ou acyle inférieur, et que R_1 et R_2 soient liés à l'acide aminé N-terminal dudit peptide, et à condition en outre que lorsque l'un des substituants R_1 ou R_2 est COE_1, l'autre doit être H.

6. Composé selon la revendication 5, dans lequel

A^0 = Gly, D-Phe ou est délété ;
A^2 = Leu, Gln, His, 1-méthyl-His ou 3-méthyl-His ;
A^4 = Ala ;
A^5 = Val ;
A^6 = Sar, Gly, D-Phe, N-méthyl-D-Ala ou D-Ala ;
A^7 = His ;

où
Z_1 est le groupe identificateur de l'un quelconque des acides aminés Leu, F_5-Phe ou p-X-Phe (où X = H, F, Cl, Br, NO_2, OH ou CH_3) et chacun des substituants Z_2, Z_3 et Z_4, indépendamment, est H, alkyle inférieur, phénylalkyle inférieur ou naphtylalkyle inférieur; et chaque substituant R_1 et R_2, indépendamment, est H, alkyle inférieur ou acyle inférieur.

7. Composé comprenant un peptide ayant 7 ou 8 résidus d'acides aminés, ou un sel pharmaceutiquement acceptable de celui-ci, ledit peptide étant un analogue de l'un des peptides naturels suivants qui se terminent au niveau de l'extrémité carboxy-terminale par un résidu Met: (a) la litorine, (b) la région carboxy-terminale de 10 acides aminés du peptide libérant la gastrine de mammifère, et (c) la région carboxy-terminale de 10 acides aminés de la bombésine d'amphibien, ledit peptide étant de formule :



dans laquelle

A^0 = Gly, Nle, acide α-aminobutyrique ou l'isomère D de l'un quelconque des acides aminés Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal, ou est délété ;
A^1 = F_5-D-Phe ;
A^2 = Gly, Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys, β-Nal, His, 1-méthyl-His ou 3-méthyl-His ;
A^4 = Ala, Val, Gln, Asn, Gly, Leu, Ile, Me, acide α-aminobutyrique, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal ;
A^5 = Gln, Asn, Gly, Ala, Leu, ne, Nle, acide α-aminobutyrique, Met, Val, p-X-Phe (où X = F, Cl, Br, OH, H ou

CH_3), Trp, Thr ou β-Nal ;
A^6 = Sar, Gly, Ala, N-méthyl-Ala, Val, Gln, Asn, Leu, Ile, Met, p-X-Phe (où X = F, Cl, Br, NO_2, OH, H ou CH_3), Trp, Cys ou β-Nal ;
A^7 = 1-méthyl-His, 3-méthyl-His ou His ;

où chaque substituant Z_{20} et Z_{30}, indépendamment, est H, alkyle inférieur, phénylalkyle inférieur, naphtylalkyle inférieur ;
à condition que lorsque l'un quelconque des substituants Z_{20} ou Z_{30} n'est pas H, A^7 soit His, A^6 soit Gly, A^5 soit Val, A^4 soit Ala, A^2 soit His et l'un quelconque des substituants R_1 ou R_2 ne soit pas H;
à condition également que tout atome de carbone asymétrique puisse être R, S ou un mélange racémique, et à condition en outre que chaque substituant R_1 et R_2, indépendamment, soit H, alkyle en C_1-C_{12}, phénylalkyle en C_7-C_{10}, COE_1 (où E_1 est alkyle en C_1-C_{20}, alcényle en C_3-C_{20}, alcynyle en C_3-C_{20}, phényle, naphtyle ou phénylalkyle en C_7-C_{10}), ou acyle inférieur, et que R_1 et R_2 soient liés à l'acide aminé N-terminal dudit peptide, et à condition en outre que lorsque l'un des substituants R_1 ou R_2 est COE_1, l'autre doit être H.

8. Composé selon la revendication 7, dans lequel

A^0 = Gly, D-Phe ou est délété ;
A^2 = Leu, Gln, His, 1-méthyl-His ou 3-méthyl-His ;
A^4 = Ala ;
A^5 = Val ;
A^6 = Sar, Gly, D-Phe, N-méthyl-D-Ala ou D-Ala;
A^7 = His ;

et où chaque substituant Z_{20} et Z_{30} est H, et chaque substituant R_1 et R_2, indépendamment, est H, alkyle inférieur ou acyle inférieur.

9. Composé selon l'une quelconque des revendications 1, 3, 5 et 7, dans lequel ledit analogue est homologue à raison d'au moins 25 %, et de préférence homologue à raison d'au moins 50 %, de la litorine, du peptide libérant la gastrine de mammifère ou de la bombésine d'amphibien.

10. Composé selon la revendication 3, dans lequel R_4 est CH_2-NH et l'atome de carbone lié à Z_2 est de configuration R.

11. Composé selon la revendication 1, dans lequel V est OR_4, et R_4 est l'un quelconque des groupes alkyle en C_1-C_{20}, alcényle en C_3-C_{20}, alcynyle en C_3-C_{20}, phényle, naphtyle ou phénylalkyle en C_7-C_{10}.

12. Composé selon la revendication 11, dans lequel ledit peptide a la formule :
D-F_5-Phe-Gln-Trp-Ala-Val-D-Ala-His-Leu-méthylester.

FIG. 1

Litorin

A1	A2	A3	A4	A5	A6	A7	A8	A9
pGlu-	Gln-	Trp-	Ala-	Val-	Gly-	His-	Phe-	Met
								W

Neuromedin C

A0	A1	A2	A3	A4	A5	A6	A7	A8	A9
Gly-	Ser-	His-	Trp-	Ala-	Val-	Gly-	His-	Leu-	Met
									W

Bombesin (last 10 amino acids)

A0	A1	A2	A3	A4	A5	A6	A7	A8	A9
Gly-	Asn-	Gln-	Trp-	Ala-	Val-	Gly-	His-	Leu-	Met
									W

human GRP (last 10 amino acids)

A0	A1	A2	A3	A4	A5	A6	A7	A8	A9
Gly-	Asn-	His-	Trp-	Ala-	Val-	Gly-	His-	Leu-	Met
									W